REMARKS

Claims under Consideration

Claims 1, 2, 4-10, 12, and 14-24 are pending in the application. Of these, claims 9 and 19 have been withdrawn from consideration, due to a restriction requirement. The examination of the remaining claims is limited by the election of species, wherein Applicants elected the c-mpl embodiment without traverse. Claims 1, 4-8, 10, 14-18, 20, 23, and 24 stand rejected under 35 U.S.C. § 112, first paragraph, claims 1, 2, 4, 6-8, 20, and 23 are rejected under 35 U.S.C. § 103, and claims 1, 4, and 23 are provisionally rejected under 35 U.S.C. § 101. Applicants address each of these rejections as follows.

Claim Amendments

Solely to expedite prosecution, Applicants have amended independent claims 1 and 10 to include the features of claims 2 and 12, respectively. In view of this amendment, claims 2 and 12 have been canceled.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1, 4-8, 10, 14-18, 20, and 23-24 are rejected under 35 U.S.C. § 112, first paragraph, for an asserted lack of enablement and claims 1, 4-8, 14-18, 20, and 23-24 are rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement.

Enablement

Claims 1, 4-8, 10, 14-18, 20, and 23-24 are rejected under 35 U.S.C. § 112, first paragraph, on enablement grounds. In particular, the Office states (page 3):

> [T]he specification, while being enabled for chimeric proteins comprising a ligand binding domain of a steroid hormone receptor and c-mpl, does not reasonably provide enablement for chimeric proteins comprising any cytokine receptor or any part of a cytokine receptor that imparts proliferation activity to a cell.

Applicants have amended claims 1 and 10 to incorporate the features of claims 2 and 12, respectively (which are not included in the 35 U.S.C. § 112, first paragraph, rejection). Claims 1 and 10 now recite that the fusion protein includes c-mpl or a proliferation inducing part of c-mpl. The present claims are clearly enabled by Applicants' specification.

The Office states that the specification is enabling for "chimeric proteins comprising a ligand binding domain of a steroid hormone receptor and c-mpl." Applicants note that the specification also provides numerous examples of assaying cell proliferation (see, for example, page 13, line 12, to page 15, line 12, page 23, line 21, to page 25, line 12, and page 31, line 14, to page 33, line 9, of the specification), of constructing vectors containing parts of c-mpl (see, for example, page 28, line 23, to page 31, line 1, of the specification), and of testing the effect on cell proliferation of fusion proteins expressed by these vectors (see, for example, page 31, line 14, to page 33, line 9, of the specification. These techniques are standard in the art and, given Applicants'

specific examples of vectors expressing a fusion protein containing a proliferation inducing part of c-mpl, Applicants submit that the full scope of the present claims is enabled by the specification. This basis for the § 112 rejection should be withdrawn.

Written Description

Claims 1, 4-8, 14-18, 20, and 23-24 are rejected under 35 U.S.C. § 112, first paragraph, for an asserted lack of written description in the specification. The Office states (page 5):

> [T]here is substantial structural diversity amongst the different families of cytokine receptors, and proteins classified as cytokine receptors are not predictably activated by dimerization, nor do they predictably induce proliferation.

As noted above, claims 1 and 10 have been amended to recite that the fusion protein includes c-mpl or a proliferation inducing part of c-mpl. Applicants' specification meets the written description standard for the fusion proteins and vectors encompassed by the present claims, as amended. In particular, fusion proteins containing a ligand-binding domain of a steroid hormone receptor and c-mpl, or a proliferation inducing part thereof, and vectors expressing such fusion proteins, are described in Applicants' specification, for example, at page 28, line 23, to page 33, line 9. Given that the specification provides specific examples of the claimed fusion proteins and vectors one skilled in the art would recognize whether a fusion protein or vector is encompassed by the present claims. This basis of the 35 U.S.C. § 112, first paragraph, rejection should also be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claims 1, 2, 4, 6-8, 20, and 23 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Gurney *et al.* and Wang *et al.* For the following reasons, Applicants respectfully traverse this rejection.

In characterizing the Gurney reference, the Office states:

> Gurney *et al.* teach a chimeric receptor comprising GHR [growth hormone receptor] fused to c-Mpl. Gurney *et al.* also teach that growth hormone induces homodimerization of the GHR, and homodimerization of c-Mpl is sufficient for receptor activity (p. 5296, column 1). However, Gurney *et al.* do not [teach] the use of an estrogen receptor instead of GHR.

Office Action mailed October 31, 2003, at p.8.

The Office further found that Wang *et al.* teach that "estrogen induces homodimerization of estrogen receptors (p. 23323, column 1)." *Id.* Based on these references, the Office concluded that "the invention taken as a whole is *prima facie* obvious over the prior art." In reaching this conclusion, the Office explained:

> Considering that the estrogen receptors are able to form homodimers after binding to estrogen, a person of ordinary skill in the art would have expected that estrogen receptors would be a useful substitution for the GHR taught by Gurney et al. Because estrogen receptors form homodimers after binding to estrogen, a person of ordinary skill in the art would have been motivated to combine the teachings of Gurney *et al.* and Wang *et al.*

Id.

In maintaining the §103 rejection in the current Office Action, the Office reasoned:

> Gurney *et al.* did not combine two cytokine receptors merely

> because they are similar to each other. Rather, Gurney *et al.* used the growth hormone receptor (GHR) in the fusion protein because GHR "is one of the best characterized members of the cytokine receptor family" and "GH (growth hormone) induces homodimerization of the receptor" (p. 5926, column 1). In order to characterize the proliferation activity of the intracellular domain of c-mpl, which must be in the dimer form in order for it to be active, Gurney *et al.* engineered the GHR-c-mpl fusion protein so that dimerization of c-mpl could be induced by GH . . . . . Wang *et al.*, however, teach that estrogen receptors form homodimers upon binding to estradiol-17B, tamoxifen, or ICI 182,780. It would have been obvious to one of ordinary skill in the art to fuse c-mpl to any ligand-binding domain that forms homodimers in order to study the proliferation activity of c-mpl.

Office Action mailed July 27, 2004, at p. 6.

Applicants' application includes claims directed to various embodiments of a fusion protein that includes a steroid hormone receptor and c-mpl. Though the claims vary, independent claims 1 and 10 are representative:

> 1. A fusion protein comprising (a) a first polypeptide and (b) a second polypeptide, wherein said first polypeptide comprises a ligand-binding domain of a steroid hormone receptor that, upon ligand binding, dimerizes, and wherein said second polypeptide comprises c-mpl, or a proliferation inducing part thereof that, upon said dimerization of said first polypeptide, imparts proliferation activity to a cell.

> 10. A vector comprising a desired exogenous gene and a DNA encoding a fusion protein comprising (a) a first polypeptide and (b) a second polypeptide, wherein said first polypeptide comprises a ligand-binding domain of a steroid hormone receptor that, upon ligand binding, dimerizes, and wherein said second polypeptide comprises a c-mpl, or a proliferation inducing part thereof that, upon said dimerization of said first polypeptide, imparts proliferation activity to a cell.

In determining whether an invention is obvious, the Examiner must determine if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103. The factual inquiries underlying obviousness include (1) the scope and content of the prior art, (2) the differences between the prior art and the claims at issue, (3) the level of ordinary skill in the art at the time the invention was made, and (4) any objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966). "The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art." *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Obviousness requires one of ordinary skill in the art have a reasonable expectation of success as to the invention--"obvious to try" and "absolute predictability" are incorrect standards. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988).

The Federal Circuit has further stated:

> "[V]irtually all [inventions] are combinations of old elements." Therefore an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention.

> Such an approach would be "an illogical and inappropriate process by which to determine patentability." *In re Rouffet*, 149 F.3d 1350, 1357-58, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998) (internal citations omitted).

Moreover, the court has explained that "[t]o prevent the use of hindsight based on the invention to defeat patentability of the invention, ... the examiner [is required] to show a motivation to combine the references that create the case of obviousness." *In re Rouffet*, 149 F.3d 1350, 1357-58, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998). Simply put, in order to establish a *prima facie* case of obviousness, "the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *In re Rouffet*, 149 F.3d 1350, 1357-58, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998). As explained below, the Office has failed to show a *prima facie* case of obviousness and the rejection should be withdrawn.

As motivation for combining the Gurney and Wang references, the Office states that "[b]ecause estrogen receptors form homodimers after binding to estrogen, a person of ordinary skill in the art would have been motivated to combine the teachings of Gurney *et al.* and Wang *et al.*" There is, however, nothing in the references of record that provides any basis for selecting a steroid hormone receptor as a component of the claimed fusion proteins, whether or not steroid hormone receptors form homodimers.

First, the Office's statement that "it would have been obvious to one of ordinary skill in the art to fuse c-mpl to any ligand that forms homodimers in order to study the

proliferation activity of c-mpl," is plainly predicated on an improper "obvious to try" standard. It is insufficient that one skilled in the art might find it "obvious to try" combining the Gurney and Wang references. As the Federal Circuit has held, an obvious to try situation does not render a claim "obvious" within the meaning of section 103. ("An invention is obvious to try rather than obvious within the meaning of § 103 ""where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful."" *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)).)

It is undisputed that neither Gurney nor Wang contains an express suggestion that a steroid hormone receptor should be used in combination with c-mpl. Moreover, nothing in the Gurney or Wang references would have suggested to a person of ordinary skill in the art that a steroid hormone receptor, upon homodimerization, would function, in combination, with c-mpl in making a fusion protein as claimed. The Office, apart from pointing out that Wang's estrogen receptor like Gurney's growth hormone receptor forms a homodimer, provides no scientific evidence or reasoning that there would have been a "reasonable expectation of success" in creating a functional fusion protein that included a steroid hormone receptor fused to c-mpl as opposed to some other receptor homodimer known in the art. Gurney's GHR was simply one of many possible receptors that were experimented with in 1995.

Why then substitute GHR for a steroid hormone receptor? And how does one decide to choose a steroid hormone receptor from among many possible homodimers? The Office assumes that the ability of the steroid hormone receptor, in combination, with a cytokine receptor such as c-mpl may be equated with the GHR:c-mpl fusion protein. There is nothing in Gurney or Wang that teaches, suggests, or motivates the skilled worker to substitute GHR for a steroid hormone receptor such as the estrogen receptor. Gurney and Wang simply describe fusion proteins, and each fails to describe or even mention substituting one homodimerizing receptor for another, much less provide a reason for doing so. Furthermore, the Office fails to explain, when analyzing the references and homodimer formation, "what specific understanding or technical principle ... would have suggested the combination." *See Rouffet*, 149 F.3d at 1357, 47 USPQ2d at 1459. Accordingly, to the extent that the Office relies upon Gurney and Wang to establish that it would have been obvious to use the steroid hormone receptor, merely because it would be obvious to try such an experiment "to study the proliferation activity of c-mpl," the Office is in error. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1367, 1380, 231 USPQ 81, 91 (Fed. Cir. 1986) *cert. denied*, 480 U.S. 947 (1987). ("Obvious to try" is improper consideration in adjudicating obviousness issue.)

The Office's rejection is plainly based on an unsupported assumption, or alternatively, unsupported finding, as to the second Graham factor: the difference between the prior art and the claims at issue, as viewed from the vantage point of one of

ordinary skill in the art. The Office's rejection reveals an implicit assumption that one of ordinary skill in the art would have perceived the difference between the disclosed fusion proteins that include a steroid hormone receptor and GHR, as disclosed by Gurney, to be insignificant. Even assuming that this implicit assumption constituted an actual "finding" by the Office, it is unsupported by any evidence, let alone substantial evidence, that one of ordinary skill in the art would have agreed that the mere disclosure of Gurney's GHR:c-mpl fusion protein would have led one of ordinary skill in the art to believe that a steroid hormone:c-mpl fusion protein would be functional.

Furthermore, no scientific basis is provided for explaining why homodimerizing receptors are interchangeable. Applicants note that growth hormone receptors and steroid hormone receptors are not structurally or functionally similar, much less interchangeable. For example, unlike growth hormone receptors, that span the plasma membrane and bind ligand outside the cell, steroid hormone receptors are found in the cytosol and the nucleus. In addition, the Office fails to explain why c-mpl dimerization would be induced by a steroid hormone receptor upon ligand binding.

Against this background, the Office reasons that a person of ordinary skill in the art would have expected that a steroid hormone receptor such as an estrogen receptor would be a useful substitution for the GHR c-mpl fusion protein taught by Gurney et al. This reasoning, as discussed above, is based on the notion that estrogen receptors like growth hormone receptors form homodimers, and that there is little difference between

these receptors. The Office provides no evidence that such a steroid hormone receptor, like a growth hormone receptor, would function in the same manner when fused to c-mpl. Without proof, there is no reason for accepting the Office's proposition that a skilled worker would make the assumption pivotal to the rejection, and the rejection is therefore unsupported.

A reference-by-reference, limitation-by-limitation analysis, as presented in the Office Action, fails to demonstrate how the Gurney and Wang references teach or suggest their combination to engineer the claimed fusion protein compositions. The obviousness analysis in the Office Action is limited to a discussion of how the references can be pieced together, in hindsight, to yield the claimed invention. It is an error to reconstruct the patentee's claimed invention from the prior art by using the patentee's claim as a "blueprint." As the Federal Circuit stated in *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir. 1985):

> When prior art references require selective combination to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself. There must be "something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. [citations omitted.]

To believe that one skilled in the art would be motivated to engineer Applicants' claimed fusion protein, when Gurney and Wang, either alone or in combination, never even discuss, suggest, or mention modifying either the GHR:c-mpl fusion or the estrogen receptor fusion protein (or even to substitute one homodimer receptor for another) in a

way that would lead one to Applicants' claimed fusion protein is to assume a level of inspiration constituting inventive activity. The case law makes clear that to avoid a hindsight-based obviousness analysis that the Patent Office bears the burden of elucidating factual teachings, suggestions, or incentives from the prior art that show the suitability of the combination of references. *See Graham v. John Deere Co.*, 383 U.S. 1, 18, 148 USPQ 459, 467 (1966) ("strict observance" of factual predicates to obviousness conclusion required).

In conclusion, the Office's finding of obviousness is neither supported by a scientifically reasoned basis, nor substantial evidence. The Office has not shown a proper *prima facie* case of obviousness, and the rejection of the claims under § 103 for obviousness over Gurney in view of Wang should therefore be withdrawn.

Double-Patenting

Claims 1, 4, and 23 are provisionally rejected under 35 U.S.C. § 101 as being the same as claims 1 and 3 of co-pending application number 09/142,305. Claim 1, as amended, is not identical to any of the claims pending in the 09/142,305 application and claims 4 and 23 depend from claim 1. Accordingly, the provisional double-patenting rejection should be withdrawn.

CONCLUSION

Applicants submit that the application is in condition for allowance, and this action is hereby respectfully requested.

Enclosed are a Petition to extend the period for replying to the Office Action for one (1) month, to and including November 29, 2004 (November 27, 2004 being a Saturday), and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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James D. DeCamp, Ph.D.
Reg. No. 43,580

JAN M. TITTEL, PH.D.
Reg. No. 52,290

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045